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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61N 1/30 — A1

(11) International Publication Number: **WO 00/44438**

(43) International Publication Date: 3 August 2000 (03.08.00)

(21) International Application Number: PCT/US00/00014

(22) International Filing Date: 12 January 2000 (12.01.00)

(30) Priority Data:
60/117,755 28 January 1999 (28.01.99) US

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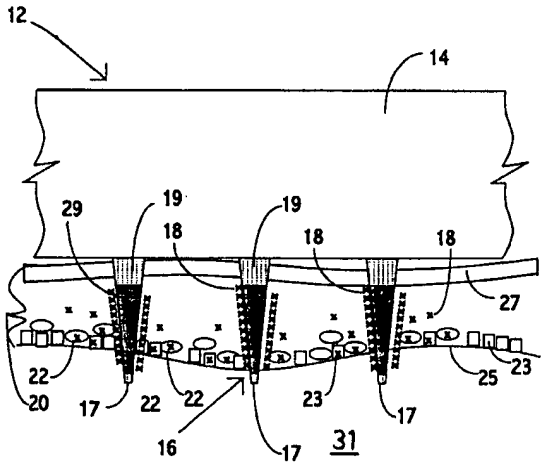
(81) Designated States: CA, CN, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: DELIVERY OF MACROMOLECULES INTO CELLS



(57) Abstract

An object of the invention is to provide a method for delivery of macromolecules into biological cells, such as Langerhans cells (22) in the epidermis (20) of a patient, which includes the steps of coating electodes (16) in an electrode assembly (12) with solid phase macromolecules to be delivered, such as a DNA, and/or RNA vaccine or a protein-based vaccine, attaching the electrode assembly (12) having the coated electrodes (16) to an electrode assembly holder (13), providing a waveform generator (15), establishing electrically conductive pathways between the electrodes (16), and the waveform generator (15), locating the electrodes (16) such that the biological cells are situated therebetween, such as by penetrating the needle electrode (16) into the epidermis (20) above the epidermal basal lamina, and providing pulse waveform from the waveform generator (15) to the electrodes (16), such that macromolecule on the electrodes (16) is driven off of the electrodes (16), and delivered into the biological cells, such as the Langerhans cells (22).

Claims

What is claimed is:

1. A method for delivery of molecules into biological cells, comprising the steps of:

coating electrodes in an electrode assembly with the molecules to be delivered,

attaching the electrode assembly having coated electrodes to an electrode assembly holder,

providing a waveform generator,

establishing electrically conductive pathways between the electrodes and the waveform generator,

locating the electrodes such that the biological cells are situated therebetween, and

providing pulse waveforms from the waveform generator to the electrodes, such that molecules on the electrodes are driven off of the electrodes and delivered into the biological cells.

2. The method of claim 1 wherein the electrodes are in a form of needle electrodes.

3. The method of claim 1 wherein the molecules are delivered into the biological cells using pulse waveforms which have an absolute voltage in a range of from 0.1 to 1,000 volts.

4. The method of claim 1 wherein the molecules are delivered with reduced sensation in a patient to Langerhans cells in epidermal tissue of the patient, wherein the pulse waveforms have an absolute applied voltage in a range of 0.1 to 300 volts, wherein electrodes of opposite polarity are separated by a separation distance in a range of from 50 to 500 microns, and wherein the electrodes are penetrated into the epidermal tissue up to and slightly beyond the basal lamina layer of the epidermal tissue.

5. The method of claim 1 wherein the pulse waveforms which drive the coating molecules off of the electrodes are electrophoresis waveforms.

6. The method of claim 1 wherein the pulse waveforms which drive the coating molecules off of the electrodes are electrophoresis waveforms in a range of from 0.1 to 100 volts/cm..

7. The method of claim 1 wherein the pulse waveforms which deliver the driven-off molecules into the biological cells are electroporation waveforms.

8. The method of claim 1 wherein the pulse waveforms which deliver the driven-off molecules into the biological cells are electroporation waveforms in a range of from 100 to 20,000 volts/cm..

9. The method of claim 1 wherein common pulse waveforms both drive the coating molecules off of the electrodes and deliver the driven-off molecules into the biological cells.

10. The method of claim 1 wherein the biological cells are in vivo.

11. The method of claim 1 wherein the biological cells are ex vivo.

12. The method of claim 1 wherein the biological cells are in vitro.

13. The method of claim 1 wherein the biological cells are in epidermal tissue.

14. The method of claim 1 wherein the biological cells are Langerhans cells in the epidermal tissue.

15. The method of claim 1 wherein the pulse waveforms are provided by applying a sequence of at least three single, operator-controlled, independently programmed, DC electrical pulses, to the biological cells, wherein the sequence of at least three DC electrical pulses has one, two, or three of the following characteristics: (a) at least two of the at least three pulses differ from each other in pulse amplitude; (b) at least two of the at least three pulses differ from each other in pulse width; and (c) a first pulse interval for a first set of two of the at least three pulses is different from a second pulse interval for a second set of two of the at least three pulses.

16. The method of claim 1, further including:

providing the electrode assembly holder with electrically conductive pathways between the electrode assembly and the waveform generator.

17. The method of claim 1, further including:

providing the electrode assembly in a sterile package, and

removing the electrode assembly from the sterile package prior to use.

18. The method of claim 1, further including:

providing the electrodes with electrically insulated outer surface electrode tip portions.

19. The method of claim 1, further including:

providing the electrodes with electrically insulated outer surface electrode base portions.

20. The method of claim 1 wherein the molecules in the electrode coating are in a solid phase.

21. The method of claim 1 wherein the molecules in the electrode coating are macromolecules.

22. The method of claim 1 wherein the macromolecules in the electrode coating include a polynucleotide vaccine.

23. The method of claim 1 wherein the macromolecules in the electrode coating include a solid phase polynucleotide vaccine.

24. The method of claim 1 wherein the macromolecules in the electrode coating include a DNA vaccine.

25. The method of claim 1 wherein the macromolecules in the electrode coating include a solid phase DNA vaccine.

26. The method of claim 1 wherein the macromolecules in the electrode coating include a RNA vaccine.

27. The method of claim 1 wherein the macromolecules in the electrode coating include a solid phase RNA vaccine.

28. The method of claim 1 wherein the macromolecules in the electrode coating include a protein-based vaccine.

29. The method of claim 1 wherein the macromolecules in the electrode coating include a solid phase protein-based vaccine.

30. The method of claim 1 wherein coating of the electrodes in the electrode assembly with the molecules to

be delivered to the biological cells is carried out by the following steps:

preparing a liquid medium in which a quantity of the molecules are carried,

contacting the electrodes with the prepared medium, and

removing the electrodes from the medium and drying off the medium, such that a coating of the molecules remains on the electrodes.

31. The method of claim 1 wherein coating of the electrodes in the electrode assembly with the molecules to be delivered to the biological cells is carried out by the following steps:

preparing a liquid medium in which a quantity of the molecules are carried,

contacting the electrodes with the prepared medium,

applying pulse waveforms to the electrodes, such that a portion of the molecules are bound to the electrodes, and

removing the electrodes from the medium and drying off the medium, such that a coating of the molecules remains on the electrodes.

32. A method for delivery of polynucleotide vaccine into Langerhans cells in the epidermis of a patient, comprising the steps of:

coating electrodes in an electrode assembly with solid phase polynucleotide vaccine,

attaching the electrode assembly having coated electrodes to an electrode assembly holder,

providing a waveform generator,

establishing electrically conductive pathways between the electrodes and the waveform generator,

locating the electrodes such that the Langerhans cells are situated therebetween, and

providing pulse waveforms from the waveform generator to the electrodes, such that polynucleotide vaccine on the electrodes are driven off of the electrodes and delivered into the Langerhans cells.

33. An apparatus for delivery of molecules into biological cells, comprising:

a waveform generator which provides pulse waveforms,

an electrode assembly holder,

an electrode assembly which is mechanically supported by said electrode assembly holder and which is electrically connected to said waveform generator through electrically conductive pathways, wherein said electrode assembly includes electrodes which are coated with the molecules to be delivered into the biological cells.

34. The apparatus of claim 33 wherein said electrode assembly is removable and replaceable from said electrode assembly holder.

35. The apparatus of claim 33 wherein:

said electrode assembly includes electrode-assembly-conductive strips, and

said electrode assembly holder includes holder conductors which are registrable with said electrode-assembly-conductive strips when said electrode assembly is mechanically connected to said electrode assembly holder, and wherein said electrode assembly holder includes electrically conductive pathways between said holder conductors and said waveform generator.

36. The apparatus of claim 33, further including:

sterile packaging for said electrode assembly which is removed from said electrode assembly after said electrode assembly is mechanically supported by said

electrode assembly holder and is electrically connected to said waveform generator.

37. The apparatus of claim 33 wherein said waveform generator provides pulse waveforms which include a sequence of at least three single, operator-controlled, independently programmed, DC electrical pulses, to the biological cells wherein the sequence of at least three DC electrical pulses has one, two, or three of the following characteristics: (a) at least two of the at least three pulses differ from each other in pulse amplitude; (b) at least two of the at least three pulses differ from each other in pulse width; and (c) a first pulse interval for a first set of two of the at least three pulses is different from a second pulse interval for a second set of two of the at least three pulses.

38. The apparatus of claim 33 wherein said electrodes are in a form of needle electrodes.

39. The apparatus of claim 33 wherein said electrodes include electrically insulated outer surface electrode tip portions and electrically insulated outer surface electrode base portions.

40. The apparatus of claim 33 wherein said electrodes are coated with macromolecules.

41. The apparatus of claim 40 wherein said macromolecules include a polynucleotide vaccine.

42. The apparatus of claim 40 wherein said macromolecules include a solid phase polynucleotide vaccine.

43. The apparatus of claim 40 wherein said macromolecules include a DNA vaccine.

44. The apparatus of claim 40 wherein said macromolecules include a solid phase DNA vaccine.

45. The apparatus of claim 40 wherein said macromolecules include a RNA vaccine.

46. The apparatus of claim 40 wherein said macromolecules include a solid phase RNA vaccine.

47. The apparatus of claim 40 wherein said macromolecules include a protein-based vaccine.

48. The apparatus of claim 40 wherein said macromolecules include a solid phase protein-based vaccine.

49. An apparatus for delivery of molecules into biological cells, comprising:

a waveform generator which provides pulse waveforms,

an electrode assembly holder, and

an electrode assembly which is mechanically supported by said electrode assembly holder and which is electrically connected to said waveform generator through electrically conductive pathways, wherein said electrode assembly includes electrodes which are coated with the molecules to be delivered into the biological cells, wherein said electrodes are coated with a solid phase DNA vaccine.

50. A packaged sterile electrode assembly which includes:

a sterile electrode assembly which includes electrodes which are coated with the molecules to be delivered into biological cells, wherein said electrode assembly includes electrode-assembly-conductive strips for

connection to electrically conductive pathways to said waveform generator, and

an internally sterile package which encloses said sterile electrode assembly contained therein.

51. The packaged sterile electrode assembly of claim 50 wherein said electrodes include electrically insulated outer surface electrode tip portions and electrically insulated outer surface electrode base portions.

52. The packaged sterile electrode assembly of claim 50 wherein said electrodes are in a form of needle electrodes.

53. The packaged sterile electrode assembly of claim 50 wherein said electrodes are coated with macromolecules.

54. The packaged sterile electrode assembly of claim 53 wherein said macromolecules include a polynucleotide vaccine.

55. The packaged sterile electrode assembly of claim 53 wherein said macromolecules include a solid phase polynucleotide vaccine.

56. The packaged sterile electrode assembly of claim 53 wherein said macromolecules include a DNA vaccine.

57. The packaged sterile electrode assembly of claim 53 wherein said macromolecules include a solid phase DNA vaccine.

58. The packaged sterile electrode assembly of claim 53 wherein said macromolecules include a RNA vaccine.

59. The packaged sterile electrode assembly of claim 53 wherein said macromolecules include a solid phase RNA vaccine.

60. The packaged sterile electrode assembly of claim 53 wherein said macromolecules include a protein-based vaccine.

61. The packaged sterile electrode assembly of claim 53 wherein said macromolecules include a solid phase protein-based vaccine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/00014

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61N 1/30
US CL :604/ 19-21, 501

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/ 19-21, 501

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 5,964,726 A (KORENSTEIN et al.) 12 October 1999, entire document.	1-61
A,P	US 5,993,434 A (DEV et al.) 30 November 1999, entire document.	1-61
A	US 4,832,682 A (SARNOFF) 23 May 1989, entire document.	1-61

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 APRIL 2000	Date of mailing of the international search report 11 MAY 2000
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